

TERIS Summary

TERIS Agent Number: 6805
Agent Name: **SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2**

Bibliographic Search Date: 12/2022

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a coronavirus that causes the infectious respiratory disease known as COVID-19.

Magnitude of Teratogenic Risk to Child Born After Exposure During Gestation: UNLIKELY

Quality and Quantity of Data on Which Risk Estimate is Based: FAIR

Comments:

- 1) INFECTION WITH SARS-CoV-2 DURING THE FIRST TRIMESTER OF PREGNANCY IS UNLIKELY TO POSE A SUBSTANTIAL TERATOGENIC RISK, BUT THE DATA ARE INSUFFICIENT TO STATE THAT THERE IS NO RISK.
- 2) TRANSPLACENTAL TRANSMISSION OF SARS-CoV-2 HAS BEEN DEMONSTRATED BUT APPEARS TO BE RARE (SEE BELOW).
- 3) SYMPTOMATIC COVID-19 DISEASE IN INFANTS WITH DOCUMENTED SARS-CoV-2 TRANSPLACENTAL INFECTION APPEARS TO BE INFREQUENT.
- 4) NEONATAL ILLNESS, AND PERINATAL DEATH WERE UNUSUALLY FREQUENT IN SOME STUDIES OF INFANTS OF WOMEN WITH COVID-19 OR SARS-CoV-2 INFECTION (SEE BELOW).
- 5) THE RISK OF PREMATURE DELIVERY APPEARS TO BE ELEVATED IN PREGNANT WOMEN WITH SARS-CoV-2 INFECTION, ESPECIALLY IF THEY HAVE COVID-19, BUT IT IS NOT CLEAR WHETHER THIS IS A RESULT OF THE INFECTION OR OF MEDICAL MANAGEMENT OF THE MOTHER'S PREGNANCY AND ILLNESS (SEE BELOW).

Summary of Teratology Studies:

MAJOR CONGENITAL ANOMALIES

The frequency of major congenital anomalies among 92 infants born to women who tested positive for SARS-CoV-2 in the first trimester was not significantly different from that reported by 292 mothers with negative SARS-CoV-2 tests during pregnancy in a cohort study that required women to self-enroll and report on their exposure and outcome (relative risk=1.2, 95% confidence interval 0.3-4.2) (Hernandez-Diaz et al., 2022). No specific pattern of malformations was observed in this study. No difference was noted between the incidence of congenital malformations among infants of mothers who tested positive for SARS-CoV-2 in the first trimester of pregnancy (1/16) compared to that of infants in mothers who tested negative for COVID-19 (7/105) in another prospective cohort study (Cosma et al., 2022). The rates of fetal malformations and abnormal fetal growth were similar on second-trimester ultrasound scans among 80 pregnant women who tested positive for SARS-CoV-2 in the first trimester and 460 pregnant women who tested negative in a Spanish population-based prospective cohort study (Crovetto et al., 2021).

In a longitudinal surveillance study of pregnant women and their infants, 88 (2.8%) of 3119 liveborn infants of women with SARS-CoV-2 infection during the first trimester of pregnancy had a major congenital anomaly (Neelam et al., 2022). Among the individual birth defects where there were more than three cases, none were reported at a prevalence that was greater than what is expected in the general population. Congenital anomalies were reported in 119 (1.5%) of 8154 infants born to mothers with SARS-CoV-2 infection during pregnancy in the PAN-COVID United Kingdom pregnancy registry, which is comparable to the background population rate of 2.1% (Mullins et al., 2022).

Major fetal anomalies were found on serial ultrasound scans in two of 38 pregnant women hospitalized for SARS-CoV-2 infection in the first or second trimester of pregnancy. Anhydramnios and small echogenic kidneys were seen in one case and a unilateral fetal cataract in the other (Rosen et al., 2021). Both pregnancies were electively terminated, and fetal blood sampling was negative for SARS-CoV-2 in both cases. In the same study, six fetal brain MRI scans performed at 32- to 36-weeks gestation showed no evidence of abnormalities. A case report of VACTERL association was found on a routine ultrasound scan of a pregnant woman who had a SARS-CoV-2 infection around the fifth week of gestation with mild COVID-19 symptoms (Chimenea et al., 2022).

VERTICAL TRANSMISSION

In a systematic review of cohort studies that included a total of 14,518 neonates born to mothers with SARS-CoV-2 infection, the overall rate of SARS-CoV-2 positivity was 1.9% (95% confidence interval 1.3-2.66) using either reverse transcriptase polymerase chain reaction (RT-PCR) and/or SARS-CoV-2 IgM antibody, but the vertical transmission rate was less than 1% when limited to babies with antenatal or intrapartum exposure (Allotey et al., 2022).

Vertical transmission has been documented in all three trimesters of pregnancy. SARS-CoV-2 infection of the placenta and fetal tissues has been demonstrated with first-trimester maternal illness in association with fetal demise (Rana et al., 2021; Shende et al., 2021; Valdespino-Vazquez et al., 2021) suggesting the possibility that the infection caused the death of the embryo or fetus. Case reports have also described infants with evidence of third trimester transplacental SARS-CoV-2 infection and neurological dysfunction or pneumonia (Alzamora et al., 2020; Facchetti et al., 2020; Govind et al., 2020; Vivanti et al., 2020). Whether these were neonatal manifestations of COVID-19 is uncertain. One study suggested a sex-biased placental immune response to the COVID-19 virus, whereby maternal SARS-CoV-2 antibody titers were lower and antibody transfer was impaired in male fetuses compared to females (Bordt et al., 2021).

SPONTANEOUS ABORTION AND FETAL OR PERINATAL DEATH

Spontaneous abortion occurred in six (19%) of 31 women with COVID-19 in a multinational retrospective clinical series (WAPM Working Group on COVID-19, 2021) and in 15 (28.8%) of 52 women infected with SARS-CoV-2 in the first trimester in a small retrospective cohort study in Turkey (Kiremitli et al., 2022). However, in larger studies, no increased risk of pregnancy loss was reported among a total of 159 pregnant women who tested positive for SARS-CoV-2 in the first trimester compared to 1774 women who tested negative in two prospective cohort studies from Denmark and Spain (Crovetto et al., 2021; la Cour Freiesleben et al., 2021). No significant increase in the rate of self-reported spontaneous abortion was reported among 77 women with presumed COVID-19 infection in the first trimester compared to 2669 who were not infected in a nationwide prospective cohort study in the United Kingdom (Balachandren et al., 2022). No significant difference in the cumulative incidence of COVID-19 was reported among 100 women who had a spontaneous abortion compared to 125 women who had ongoing pregnancies in a case-control study (Cosma et al., 2021). The incidence of spontaneous abortion was similar among 478 infected women with COVID-19 in the first trimester and a matched uninfected group in an Israeli retrospective cohort study (Fallach et al., 2022). No increased rates of spontaneous abortion were found among pregnant women infected with SARS-CoV-2 during early pregnancy in two other smaller prospective studies in the United States and Spain (Jacoby et al., 2021; Gonzalez Rodriguez et al., 2022).

A two-fold increase in risk of stillbirth was reported among 3527 women with SARS-CoV-2 infection in pregnancy compared to unaffected women (adjusted odds ratio=2.21, 95% confidence interval 1.58-3.11) in a population-based cohort study in England (Gurrol-Urganci et al., 2021). A systematic review and meta-analysis of earlier studies found a 4% (95% confidence interval 1.5-10.0%) rate of stillbirth among 989 deliveries to pregnant women with confirmed SARS-CoV-2 infection (Jafari et al., 2021). The rate of neonatal death among 2152 infants of women with SARS-CoV-2 infection during pregnancy in this study was 2.5% (95% confidence interval 1.5-6.0%). In a large COVID-19 pregnancy registry from the United Kingdom, the frequency of stillbirth was higher among 2686 participants delivering within two weeks of the infection compared to 4598 women delivering more than two weeks after COVID-19 infection (0.8% vs 0.2% (95% confidence interval 0.3-1.0) (Mullins et al., 2022). Several subsequent studies demonstrated severe placentitis with persistent histiocytic intervillousities and elevated fibrin deposition in a total of 76 stillbirths who tested positive for SARS-CoV-2 (Fitzgerald et al., 2022; Schwarts et al., 2022; Shook et al., 2022).

No significant association of maternal COVID-19 diagnosis and stillbirth was observed in a United States medical record study of 6380 women with ICD-10 or billing codes for COVID-19 among 406,446 women hospitalized for childbirth when the analysis was adjusted for age, race/ethnicity, geographic region, and 12 other covariates (odds ratio=1.23, 95% confidence interval 0.87-1.75) (Jering et al., 2021). In a Canadian observational surveillance study, the rate of stillbirth (0.61%) among 5743 pregnant women with SARS-CoV-2 infection was even lower than among unaffected pregnancies (0.83%) (relative risk=0.73, 95% confidence interval 0.50-0.99) (McClymont et al., 2022). The rate of neonatal mortality was not different among 2323 infants delivered to women who tested positive for SARS-CoV-2 in pregnancy compared to infants who were born to non-SARS-CoV-2 positive mothers in a nationwide prospective cohort study from Sweden (Norman et al., 2021). In an Israeli observational cohort study, no difference in the incidence of intrauterine fetal death was found between 943 COVID-19 infected women in the second trimester or 1332 infected women in the third trimester and their matched controlled uninfected groups (Fallach et al., 2022).

PREMATURE DELIVERY AND NEONATAL ILLNESS

Premature delivery and its associated morbidity are unusually frequent among infants whose mothers had COVID-19 or SARS-CoV-2 infections during pregnancy. In a large population-based birth cohort study in California, COVID-19 diagnosis among 8957 pregnant women was associated with a 40% increased risk of preterm birth (relative risk=1.4, 95% confidence interval 1.3-1.4) and a 60% increased risk of very preterm birth (less than 32 weeks) (relative risk=1.6, 95% confidence interval 1.4-1.9), with no effect modification reported for the overall association by race/ethnicity or insurance status (Karasek et al., 2021). A systematic review of case-control studies completed by January 2021 found increased risks for preterm birth (summary odds ratio=1.82, 95% confidence interval 1.38-2.39) and admission to the neonatal intensive care unit (summary odds ratio=3.69, 95% confidence interval 1.39-9.82) among infants whose mothers had COVID-19 or SARS-CoV-2 infections during pregnancy (Wei et al., 2021). Similar findings indicating an increased risk for preterm birth were shown in a subsequent Canadian cohort study of 5746 pregnant women with SARS-CoV-2 (relative risk=1.63, 95% confidence interval 1.52-1.76) (McClymont et al., 2022), and a United States cohort of 18,715 pregnant women with COVID-19 who were more likely to deliver preterm than unaffected pregnant women (16.4% vs. 11.5%; $p<0.001$) (Chinn et al., 2021).

In a large-scale multinational cohort study, infants born to 706 women with COVID-19 had a significantly higher severe neonatal morbidity index (relative risk=2.66, 95% confidence interval 1.69-4.18) and severe perinatal morbidity and mortality index (relative risk=2.14, 95% confidence interval 1.66-2.75) compared with newborns of 1424 women with broadly similar demographic characteristics and without COVID-19 diagnosis (Villar et al., 2021). Similar findings were reported in other smaller cohort studies (Harel et al., 2022).

The risks of prematurity and other neonatal adverse outcomes also appeared to be greater for the infants of women with severe COVID-19 in comparison to those who had mild COVID-19 or asymptomatic SARS-CoV-2 infection in several other epidemiological studies and meta-analyses (Katz et al., 2021; Lai et al., 2021; Metz et al., 2021; Vousden et al., 2021; Wei et al., 2021; Harel et al., 2022). In an earlier systematic review and meta-analysis of published studies, the pooled frequencies of preterm birth (21%, 95% confidence interval 12-34%), low birth weight (25%, 95% confidence interval 16-37%), and neonatal intensive care unit admission (17%, 95% confidence interval 11-25%) appeared to be unusually high (Jafari et al., 2021). It is not clear if these problems reflect a direct effect of maternal or infant SARS-CoV-2 infections, of their treatment, or of altered obstetrical management of the pregnancies of women with such infections. The high rate of operative delivery in the pregnancies of women with SARS-CoV-2 infections (Di Toro et al., 2021; Jafari et al., 2021) suggests that altered obstetrical management is at least a contributing factor.

FETAL GROWTH

No significant differences in head circumference, abdominal circumference, femur length, or estimated fetal weight were observed between 49 SARS-CoV-2 positive pregnancies and 98 pregnancies of uninfected women at either the second or third trimester ultrasound scans in a prospective case-control study (Rizzo et al., 2021). In the same study, no differences were noted in maternal and fetal Doppler findings between the two study groups.

EARLY CHILDHOOD DEVELOPMENT

In a prospective cohort study conducted in the United States, the frequency of adverse developmental outcomes at six months of age among infants of 114 mothers exposed to SARS-CoV-2 infection in pregnancy was not significantly different from that observed in unexposed pregnancies, regardless of timing or severity of infection (Shuffrey et al., 2022). An association of receiving a neurodevelopmental diagnosis at 12 months of age was reported among 222 children of mothers who tested positive for SARS-CoV-2 during pregnancy following adjustments for several factors including preterm delivery (adjusted odds ratio=1.86, 95% confidence interval 1.03-3.36) (Edlow et al., 2022). Maternal third trimester infection seemed to carry the highest risk in this retrospective cohort study. In contrast, the risk of social-emotional or overall developmental delay at three months of age among the infants of 57 women who contracted a SARS-CoV-2 infection during late pregnancy was not significantly increased compared to the infants of 78 women in the non-infection cohort in a prospective cohort study from China (Wu et al., 2021).

No adverse effects were found on early physical growth, hearing and neurological development among 199 infants born to mothers with SARS-CoV-2 infection in pregnancy or at delivery in a prospective longitudinal study (Buonsenso et al., 2022). In the same study, however, preliminary findings among three of 21 infants who underwent ophthalmological follow up assessment, showed certain retinal abnormalities, including bilateral choroidal perfusion anomalies, capillary obliteration, and bilateral vascular tortuosity. In an earlier Brazilian case-series, no ocular abnormalities were reported among 165 newborns of mothers with SARS-CoV-2 infection in pregnancy (Kiappe et al., 2021).

ANIMAL TERATOLOGY STUDIES

Studies of neonatal outcomes in the offspring of pregnant animals infected with SARS-CoV-2 have not been published in the peer-reviewed literature.

Selected References:

(Each paper is classified as a review [R], human case report [C], human epidemiological study [E], human clinical series [S], animal study [A], or other [O].)

Allotey J, Chatterjee S, Kew T, Gaetano A, Stallings E, Fernandez-Garcia S, Yap M, Sheikh J, Lawson H, Coomar D, Dixit A, Zhou D, Balaji R, Littmoden M, King Y, Debenham L, Llavall AC, Ansari K, Sandhu G, Banjoko A, Walker K, O'Donoghue K, van Wely M, van Leeuwen E, Kostova E, Kunst H, Khalil A, Brizuela V, Broutet N, Kara E, Kim CR, Thorson A, Oladapo OT, Zamora J, Bonet M, Mofenson L, Thangaratnam S: SARS-CoV-2 positivity in offspring and timing of mother-to-child transmission: living systematic review and meta-analysis. *BMJ* 376:e067696, 2022. [R]

Alzamora MC, Paredes T, Caceres D, Webb CM, Valdez LM, La Rosa M: Severe COVID-19 during pregnancy and possible vertical transmission. *Am J Perinatol* 37(8):861-865, 2020. [C]

Balachandren N, Davies MC, Hall JA, Stephenson JM, David AL, Barrett G, O'Neill HC, Ploubidis GB, Yasmin E, Mavrelou D: SARS-CoV-2 infection in the first trimester and the risk of early miscarriage: a UK population-based prospective cohort study of 3041 pregnancies conceived during the pandemic. *Hum Reprod* 37(6):1126-1133, 2022. [E]

Bordt EA, Shook LL, Atyeo C, Pullen KM, De Guzman RM, Meinsohn MC, Chauvin M, Fischinger S, Yockey LJ, James K, Lima R, Yonker LM, Fasano A, Brigida S, Bebell LM, Roberts DJ, Pepin D, Huh JR, Bilbo SD, Li JZ, Kaimal A, Schust DJ, Gray KJ, Lauffenburger D, Alter G, Edlow AG: Maternal SARS-CoV-2 infection elicits sexually dimorphic placental immune responses. *Sci Transl Med* 13(617):eabi7428, 2021. [E]

Buonsenso D, Costa S, Giordano L, Priolo F, Colonna AT, Morini S, Sbarbati M, Pata D, Acampora A, Conti G, Crudo F, Cantiani A, Martina BM, Amorelli GM, Orazi L, Petrianni M, Ricci D, Lanzone A, Sanguinetti M, Cattani P, Sali M, Romeo D, Zampino G, Vento G, Valentini P: Short- and mid-term multidisciplinary outcomes of newborns exposed to SARS-CoV-2 in utero or during the perinatal period: preliminary findings [published erratum appears in *Eur J Pediatr* 181(4):1521-1522, 2022]. *Eur J Pediatr* 181(4):1507-1520, 2022. [S]

Chimenea A, Garcia-Diaz L, Calderon AM, Antinolo G: Prenatal diagnosis of VACTERL association after early-first trimester SARS-CoV-2 infection. *Congenit Anom* 2022 Dec 14 (published online ahead of print). [C]

Chinn J, Sedighim S, Kirby KA, Hohmann S, Hameed AB, Jolley J, Nguyen NT: Characteristics and outcomes of women with COVID-19 giving birth at US academic centers during the COVID-19 pandemic. *JAMA Netw Open* 4(8):e2120456, 2021. [E]

Cosma S, Carosso AR, Cusato J, Borella F, Bertero L, Bovetti M, Bevilacqua F, Mengozzi G, Mazzone R, Ghisetti V, Di Perri G, Benedetto C: Obstetric and neonatal outcomes after SARS-CoV-2 infection in the first trimester of pregnancy: a prospective comparative study. *J Obstet Gynaecol Res* 48(2):393-401, 2022. [E]

Cosma S, Carosso AR, Cusato J, Borella F, Carosso M, Bovetti M, Filippini C, D'Avolio A, Ghisetti V, Di Perri G, Benedetto C: Coronavirus disease 2019 and first-trimester spontaneous abortion: a case-control study of 225 pregnant patients. *Am J Obstet Gynecol* 224(4):391.e1-391.e7, 2021. [E]

Crovetto F, Crispi F, Llorba E, Pascal R, Larroya M, Trilla C, Camacho M, Medina C, Dobano C, Gomez-Roig MD, Figueras F, Gratacos E: Impact of SARS-CoV-2 infection on pregnancy outcomes: a population-based study. *Clin Infect Dis* 73(10):1768-1775, 2021. [E]

Di Toro F, Gjoka M, Di Lorenzo G, De Santo D, De Seta F, Maso G, Risso FM, Romano F, Wiesenfeld U, Levi-D'Ancona R, Ronfani L, Ricci G: Impact of COVID-19 on maternal and neonatal outcomes: a systematic review and meta-analysis. *Clin Microbiol Infect* 27(1):36-46, 2021. [R]

Edlow AG, Castro VM, Shook LL, Kaimal AJ, Perlis RH: Neurodevelopmental outcomes at 1 year in infants of mothers who tested positive for SARS-CoV-2 during pregnancy. *JAMA Netw Open* 5(6):e2215787, 2022. [E]

Facchetti F, Bugatti M, Drea E, Tripodo C, Sartori E, Cancila V, Papaccio M, Castellani R, Casola S, Boniotti MB, Cavadini P, Lavazza A: SARS-CoV2 vertical transmission with adverse effects on the newborn revealed through integrated immunohistochemical, electron microscopy and molecular analyses of placenta. *EBioMedicine* 59:102951, 2020. [E]

Fallach N, Segal Y, Agassy J, Perez G, Peretz A, Chodick G, Gazit S, Patalon T, Ben Tov A, Goldshtein I: Pregnancy outcomes after SARS-CoV-2 infection by trimester: a large, population-based cohort study. *PLoS One* 17(7):e0270893, 2022. [E]

Fitzgerald B, O'Donoghue K, McEntagart N, Gillan JE, Kelehan P, O'Leary J, Downey P, Dean J, De Gascun CF, Birmingham J, Armstrong F, Al Fathil A, Maher N, Murphy C, Burke L: Fetal deaths in Ireland due to SARS-CoV-2 placentitis caused by SARS-CoV-2 Alpha. *Arch Pathol Lab Med* 146(5):529-537, 2022. [S]

Gonzalez Rodriguez L, Oreja Cuesta AB, Pardo Pumar MI, Ferriols-Perez E, Pedro Carulla R, Bernardo Vega R, Vaquerizo Ruiz O, de la Cruz Conty ML, Couceiro Naveira E, Marin Ortiz E, Cruz Melguizo S, Martinez-Perez O: SARS-CoV-2 infection in early first-trimester miscarriages: a prospective observational study. *Reprod Biomed Online* 44(1):127-130, 2022. [E]

Govind A, Essien S, Kartikeyan A, Fakokunde A, Janga D, Yoong W, Nakhosteen A: Re: Novel coronavirus COVID-19 in late pregnancy: outcomes of first nine cases in an inner city London hospital. *Eur J Obstet Gynecol Reprod Biol* 251:272-274, 2020. [S]

Gurol-Urganci I, Jardine JE, Carroll F, Draycott T, Dunn G, Fremeaux A, Harris T, Hawdon J, Morris E, Muller P, Waite L, Webster K, van der Meulen J, Khalil A: Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection at the time of birth in England: national cohort study. *Am J Obstet Gynecol* 225(5):522.e1-522.e11, 2021. [E]

Harel L, Eliasi E, Jaffe Lifshitz S, Schindler Y, Rosen D, Olteanu I, Rottenstreich A, Tzabari A: Does the presence of symptoms affect pregnancy outcomes in third trimester in women with SARS-CoV-2. *J Matern Fetal Neonatal Med* 35(25):7582-7589, 2022. [E]

Hernandez-Diaz S, Smith LH, Wyszynski DF, Rasmussen SA: First trimester COVID-19 and the risk of major congenital malformations- International Registry of Coronavirus Exposure in Pregnancy. *Birth Defects Res* 114(15):906-914, 2022. [E]

Jacoby VL, Murtha A, Afshar Y, Gaw S, Asiodu I, Tolosa J, Norton ME, Boscardin J, Flaherman V: Risk of pregnancy loss prior to 20 weeks gestation with COVID-19. *Am J Obstet Gynecol* 225(4):456-457, 2021. [E]

Jafari M, Pormohammad A, Sheikh Neshin SA, Ghorbani S, Bose D, Alimohammadi S, Basirjafari S, Mohammadi M, Rasmussen-Ivey C, Razizadeh MH, Nouri-Vaskeh M, Zarei M: Clinical characteristics and outcomes of pregnant women with COVID-19 and comparison with control patients: a systematic review and meta-analysis. *Rev Med Virol* 31(5):1-16, 2021. [R]

Jering KS, Claggett BL, Cunningham JW, Rosenthal N, Vardeny O, Greene MF, Solomon SD: Clinical characteristics and outcomes of hospitalized women giving birth with and without COVID-19. *JAMA Intern Med* 181(5):714-717, 2021. [E]

Karasek D, Baer RJ, McLemore MR, Bell AJ, Blebu BE, Casey JA, Coleman-Phox K, Costello JM, Felder JN, Flowers E, Fuchs JD, Gomez AM, Karvonen K, Kuppermann M, Liang L, McKenzie-Sampson S, McCulloch CE, Oltman SP, Pantell MS, Piao X, Prather AA, Schmidt RJ, Scott KA, Spellens S, Stookey JD, Tesfalul M, Rand L, Jelliffe-Pawlowski LL: The association of COVID-19 infection in pregnancy with preterm birth: a retrospective cohort study in California. *Lancet Reg Health Am* 2:100027, 2021. [E]

Katz D, Bateman BT, Kjaer K, Turner DP, Spence NZ, Habib AS, George RB, Toledano RD, Grant G, Madden HE, Butwick AJ, Lynde G, Minehart RD, Beilin Y, Houle TT, Sharpe EE, Kodali B, Bharadwaj S, Farber MK, Palanisamy A, Prabhu M, Gonzales NY, Landau R, Leffert L: The Society for Obstetric Anesthesia and Perinatology Coronavirus Disease 2019 Registry: an analysis of outcomes among pregnant women delivering during the initial severe acute respiratory syndrome coronavirus-2 outbreak in the United States. *Anesth Analg* 133(2):462-473, 2021. [E]

Kiappe OP, Santos da Cruz NF, Rosa PAC, Arrais L, Bueno de Moraes NS: Ocular assessments of a series of newborns gestationally exposed to maternal COVID-19 infection. *JAMA Ophthalmol* 139(7):777-780, 2021. [S]

Kiremitti S, Kiremitti T, Ulug P, Kirkinci A, Kurnuc FZ, Yilmaz N, Dinc K, Yilmaz BK, Gul OI, Uzel K: Does being infected with SARS-CoV-2 in the first-trimester increase the risk of miscarriage? *An Acad Bras Cienc* 94(2):e20211283, 2022. [E]

la Cour Freiesleben N, Egerup P, Hviid KVR, Severinsen ER, Kolte AM, Westergaard D, Fich Olsen L, Praetorius L, Zedeler A, Christiansen A-MH, Nielsen JR, Bang D, Berntsen S, Olle-Lopez J, Ingham A, Bello-Rodriguez J, Storm DM, Ethelberg-Findsen J, Hoffmann ER, Wilken-Jensen C, Jorgensen FS, Westh H, Jorgensen HL, Nielsen HS: SARS-CoV-2 in first trimester pregnancy: a cohort study. *Hum Reprod* 36(1):40-47, 2021. [E]

Lai J, Romero R, Tarca AL, Iliodromiti S, Rehal A, Banerjee A, Yu C, Peeva G, Palaniappan V, Tan L, Mehta M, Nicolaidis KH: SARS-CoV-2 and the subsequent development of preeclampsia and preterm birth: evidence of a dose-response relationship supporting causality. *Am J Obstet Gynecol* 225(6):689-693.e1, 2021. [E]

McClymont E, Albert AY, Alton GD, Boucoiran I, Castillo E, Fell DB, Kuret V, Poliquin V, Reeve T, Scott H, Sprague AE, Carson G, Cassell K, Crane J, Elwood C, Joynt C, Murphy P, Murphy-Kaulbeck L, Saunders S, Shah P, Snelgrove JW, van Schalkwyk J, Yudin MH, Money D: Association of SARS-CoV-2 infection during pregnancy with maternal and perinatal outcomes. *JAMA* 327(20):1983-1991, 2022. [E]

Metz TD, Clifton RG, Hughes BL, Sandoval G, Saade GR, Grobman WA, Manuck TA, Miodovnik M, Sowles A, Clark K, Gyamfi-Bannerman C, Mendez-Figueroa H, Sehdev HM, Rouse DJ, Tita ATN, Bailit J, Costantine MM, Simhan HN, Macones GA: Disease severity and perinatal outcomes of pregnant patients with coronavirus disease 2019 (COVID-19). *Obstet Gynecol* 137(4):571-580, 2021. [E]

Mullins E, Perry A, Banerjee J, Townson J, Grozeva D, Milton R, Kirby N, Playle R, Bourne T, Lees C; PAN-COVID Investigators: Pregnancy and neonatal outcomes of COVID-19: The PAN-COVID study. *Eur J Obstet Gynecol Reprod Biol* 276:161-167, 2022. [E]

Neelam V, Reeves EL, Woodworth KR, O'Malley Olsen E, Reynolds MR, Rende J, Wingate H, Manning SE, Romitti P, Ojo KD, Silcox K, Barton J, Mobley E, Longcore ND, Sokale A, Lush M, Delgado-Lopez C, Diedhiou A, Mbotha D, Simon W, Reynolds B, Hamdan TS, Beauregard S, Eillis EM, Seo JY, Bennett A, Eillington S, Hall AJ, Azziz-Baumgartner E, Tong VT, Gilboa SM: Pregnancy and infant outcomes by trimester of SARS-

CoV-2 infection in pregnancy-SET-NET, 22 jurisdictions, January 25, 2020-December 31, 2020. *Birth Defects Res* 2022 Sep 6 (published online ahead of print). [E]

Norman M, Naver L, Soderling J, Ahlberg M, Hervius Askling H, Aronsson B, Bystrom E, Jonsson J, Sengpiel V, Ludvigsson JF, Hakansson S, Stephansson O: Association of maternal SARS-CoV-2 infection in pregnancy with neonatal outcomes. *JAMA* 325(20):2076-2086, 2021. [E]

Rana MS, Usman M, Alam MM, Khalid A, Ikram A, Salman M, Zaidi SSZ, Faryal R, Qadir M, Umair M, Roohullah, Sufian MM: First trimester miscarriage in a pregnant woman infected with COVID-19 in Pakistan. *J Infect* 82(1):e27-e28, 2021. [C]

Rizzo G, Mappa I, Maqina P, Bitsadze V, Khizroeva J, Makatsarya A, D'Antonio F: Effect of SARS-CoV-2 infection during the second half of pregnancy on fetal growth and hemodynamics: a prospective study. *Acta Obstet Gynecol Scand* 100(6):1034-1039, 2021. [E]

Rosen H, Bart Y, Zlatkin R, Ben-Sira L, Ben Bashat D, Amit S, Cohen C, Regev-Yochay G, Yinon Y: Fetal and perinatal outcome following first and second trimester COVID-19 infection: evidence from a prospective cohort study. *J Clin Med* 10(10):2152, 2021. [S]

Schwartz DA, Avvad-Portari E, Babal P, Baldewijns M, Blomberg M, Bouachba A, Camacho J, Collardeau-Frachon S, Colson A, Dehaene I, Ferreres JC, Fitzgerald B, Garrido-Pontnou M, Gergis H, Hargital B, Helguera-Repetto AC, Holmstrom S, Irlles CL, Leijonhfvud A, Libbrecht S, Marton T, McEntagart N, Molina JT, Morotti R, Nadal A, Navarro A, Nelander M, Oviedo A, Otani ARO, Papadogiannakis N, Petersen AC, Roberts DJ, Saad AG, Sand A, Schoenmakers S, Sehn JK, Simpson PR, Thomas K, Valdespino-Vazquez MY, van der Meeren LE, Van Dorpe J, Verdijk RM, Watkins JC, Zaigham M. Placental tissue destruction and insufficiency from COVID-19 causes stillbirth and neonatal death from hypoxic-ischemic injury. *Arch Pathol Lab Med* 146(6):660-676, 2022. [S]

Shende P, Gaikwad P, Gandhewar M, Ukey P, Bhide A, Patel V, Bhagat S, Bhor V, Mahale S, Gajbhiye R, Modi D: Persistence of SARS-CoV-2 in the first trimester placenta leading to transplacental transmission and fetal demise from an asymptomatic mother. *Hum Reprod* 36(4):899-906, 2021. [C]

Shook LL, Brigida S, Regan J, Flynn JP, Mohammadi A, Etemad B, Siegel MR, Clapp MA, Li JZ, Roberts DJ, Edlow AG: SARS-CoV-2 placentitis associated with B.1.617.2 (delta) variant and fetal distress or demise. *J Infect Dis* 225(5):754-758, 2022. [S]

Shuffrey LC, Firestein MR, Kyle MH, Fields A, Alcantara C, Amso D, Austin J, Bain JM, Barbosa J, Bence M, Bianco C, Fernandez CR, Goldman S, Gyamfi-Bannerman C, Hott V, Hu Y, Hussain M, Factor-Litvak P, Lucchini M, Mandel A, Marsh R, McBrien D, Mourad M, Muhle R, Noble KG, Penn AA, Rodriguez C, Sania A, Silver WG, O'Reilly KC, Stockwell M, Tottenham N, Welch MG, Zork N, Fifer WP, Monk C, Dumitriu D: Association of birth during the COVID-19 pandemic with neurodevelopmental status at 6 months in infants with and without in utero exposure to maternal SARS-CoV-2 infection. *JAMA Pediatr* 176(6):e215563, 2022. [E]

Valdespino-Vazquez MY, Helguera-Repetto CA, Leon-Juarez M, Villavicencio-Carrisoza O, Flores-Pliego A, Moreno-Verduzco ER, Diaz-Perez DL, Villegas-Mota I, Carrasco-Ramirez E, Lopez-Martinez IE, Giraldo-Gomez DM, Lira R, Yocupicio-Monroy M, Rodriguez-Bosch M, Sevilla-Reyes EE, Cortes-Bonilla M, Acevedo-Gallegos S, Merchant-Larios H, Cardona-Perez JA, Irlles C: Fetal and placental infection with SARS-CoV-2 in early pregnancy. *J Med Virol* 93(7):4480-4487, 2021. [C]

Villar J, Ariff S, Gunier RB, Thiruvengadam R, Rauch S, Kholin A, Roggero P, Prefumo F, do Vale MS, Cardona-Perez JA, Maiz N, Cetin I, Savasi V, Deruelle P, Easter SR, Sichitiu J, Soto Conti CP, Ernawati E, Mhatre M, Teji JS, Liu B, Capelli C, Oberto M, Salazar L, Gravett MG, Cavoretto PI, Nachinab VB, Galadanci H, Oros D, Ayede AI, Sentilhes L, Bako B, Savorani M, Cena H, Garcia-May PK, Etuk S, Casale R, Abd-Elsalam S, Ikenoue S, Aminu MB, Vecchiarelli C, Duro EA, Usman MA, John-Akinola Y, Nieto R, Ferrazi E, Bhutta ZA, Langer A, Kennedy SH, Papageorgiou AT: Maternal and neonatal morbidity and mortality among pregnant women with and without COVID-19 infection: the INTERCOVID multinational cohort study. *JAMA Pediatr* 175(8):817-826, 2021. [E]

Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, Benachi A, De Luca D: Transplacental transmission of SARS-CoV-2 infection. *Nat Commun* 11(1):3572, 2020. [C]

Vousden N, Bunch K, Morris E, Simpson N, Gale C, O'Brien P, Quigley M, Brocklehurst P, Kurinczuk JJ, Knight M: The incidence, characteristics and outcomes of pregnant women hospitalized with symptomatic and asymptomatic SARS-CoV-2 infection in the UK from March to September 2020: a national cohort study using the UK Obstetric Surveillance System (UKOSS). *PLoS One* 16(5):e0251123, 2021. [E]

WAPM (World Association of Perinatal Medicine) Working Group on COVID-19: Maternal and perinatal outcomes of pregnant women with SARS-CoV-2 infection. *Ultrasound Obstet Gynecol* 57(2):232-241, 2021. [E]

Wei SQ, Bilodeau-Bertrand M, Liu S, Auger N: The impact of COVID-19 on pregnancy outcomes: a systematic review and meta-analysis. *CMAJ* 193(16):E540-E548, 2021. [R]

Wu T, Chen L, Wang Y, Shi H, Niu J, Yin X, Li M, Tan C, Jiang H, Zheng D, Wei Y, Zhao Y, Wang X, Qiao J: Effects of SARS-CoV-2 infection during late pregnancy on early childhood development: a prospective cohort study. *Front Pediatr* 9:750012, 2021. [E]

COVID-19 PREGNANCY STUDY

A pregnancy study has been established for women infected with, or exposed to, the SARS-CoV-2 coronavirus (which causes COVID-19) during pregnancy. All study research will be performed via phone.

Healthcare providers are encouraged to enroll such patients in the MotherToBaby Pregnancy Study by calling 877-311-8972 (<https://mothertobaby.org/join-a-study-form/>).